10/550286
JC14 Rec'd PCT/PTO 22 SEP 2005

PATENTS
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Emory University

PCT No.: PCT/US2004/009548

International Filing Date: 29 March 2004

For: HIF-1 INHIBITORS

CERTIFICATE OF EXPRESS MAIL

Mail Stop PCT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

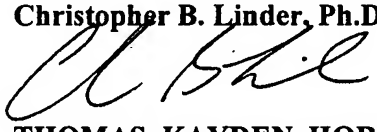
Enclosed for filing in the above case are the following documents:

Return Postcard;
Transmittal Letter;
Request for Rectification of a Change Under PCT Rule 91.1; and
Newly Renumbered Claims Set (pp. 58-81)

Further, the Commissioner is authorized to charge Deposit Account No. 20-0778 for any additional fees required. The Commissioner is requested to credit any excess fee paid to Deposit Account No. 20-0778.

Respectfully submitted,

Christopher B. Linder, Ph.D., Reg. No. 47,751



THOMAS, KAYDEN, HORSTEMEYER & RISLEY, L.L.P.
100 Galleria Parkway, N.W.
Suite 1750
Atlanta, Georgia 30339-5948

Our Docket No: **050508-2320**

I hereby certify that all correspondences listed above are being deposited for delivery to the above addressee, with the United States Postal Service **"EXPRESS MAIL POST OFFICE TO ADDRESSEE"** service under 37 CFR §1.10 on the date indicated below:

The envelope has been given U.S. Postal Service "Express Mail Post Office To Addressee" Package # **EV437537615US**.

Date: 19 August 2004

Lara L. O'Brien

JC14 Rec'd PCT/PTO 22 SEP 2005

TRANSMITTAL LETTER TO THE UNITED STATES RECEIVING OFFICE

PTO-1382 (Rev. 04-2003) (Modified) PCTUS2.FRP /REV03

Date	19 August 2004
International Application No.	PCT/US2004/009548
Attorney Docket No.	050508-2320

10/550286

I. Certification under 37 CFR 1.10 (if applicable)

EV437537615US	19 August 2004
Express Mail mailing number	Date of Deposit

I hereby certify that the application/correspondence attached hereto is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Lara L. O'Brien	Lara L. O'Brien
Signature of person mailing correspondence	Typed or printed name of person mailing correspondence

II. ☐ **New International Application**

TITLE	HIF-1 INHIBITORS	Earliest priority date (Day/Month/Year): 27 March 2003

SCREENING DISCLOSURE INFORMATION: In order to assist in screening the accompanying international application for purposes of determining whether a license for foreign transmittal should and could be granted and for other purposes, the following information is supplied. (Note: check as many boxes as apply):

A. ☐ The invention disclosed was **not** made in the United States.

B. ☐ There is no prior U.S. application relating to this invention.

C. ☐ The following prior U.S. application(s) contain subject matter which is related to the invention disclosed in the attached international application. *(NOTE: priority to these applications may or may not be claimed on form PCT/RO/101 (Request) and this listing does not constitute a claim for priority).*

application no.		filed on	
application no.		filed on	

D. ☐ The present international application contains additional subject matter not found in the prior U.S. application(s) identified in paragraph C. above. The additional subject matter is found on pages ____ and ☐ **DOES NOT ALTER** ☐ **MIGHT BE CONSIDERED TO ALTER** the general nature of the invention in a manner which would require the U.S. application to have been made available for inspection by the appropriate defense agencies under 35 U.S.C. 181 and 37 CFR 5.1. See 37 CFR 5.15.

III. ☐ **A Response to an Invitation from the RO/US.** The following document(s) is (are) enclosed:

A. ☐ A Request for An Extension of Time to File a Response

B. ☐ A Power of Attorney (General or Regular)

C. ☐ Replacement pages:

pages		of the request (PCT/RO/101)	pages		of the figures
pages		of the description	pages		of the abstract
pages		of the claims			

D. ☐ Submission of Priority Documents

Priority document		Priority document	

E. ☐ Fees as specified on attached Fee Calculation sheet form PCT/RO/101 annex

IV. ☑ **A Request for Rectification under PCT 91** ☑ **A Petition** ☐ **A Sequence Listing Diskette**

V. ☐ **Other** (please specify):

The person signing this form is the:

☐ Applicant	Christopher B. Linder
☑ Attorney/Agent (Reg. No.) 47,751	Typed name of signer
☐ Common Representative	Signature

10/550286
JC14 Rec'd PCT/PTO 22 SEP 2005

IN THE UNITED STATES RECEIVING OFFICE (RO/US)
UNDER THE PATENT COOPERATION TREATY

In Re Application of: Emory University
Int. Appln. No.: PCT/US04/09548
Int. Filing Date: 29 March 2004
Title: *HIF-1 Inhibitors*
Atty Docket No.: 050508-2320

REQUEST FOR RECTIFICATION OF A CHANGE UNDER PCT RULE 91.1

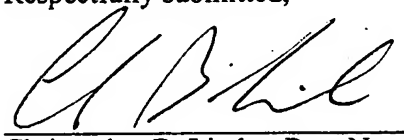
Mail Stop PCT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the *Communication in Cases For Which No Other Form is Applicable* mailed on 01 July 2004, Applicant herewith submits replacement claims 1-75. The Communication reported that claim 46 was omitted in the original application; however, the claim numbers were incorrectly numbered. Therefore, we corrected the numbering of the claims and submit a clean set of the re-numbered claims for your review (pages 58-81 of the application).

Further, the Commissioner is authorized to charge Deposit Account No. 20-0778 for any additional fees required. The Commissioner is requested to credit any excess fee paid to Deposit Account No. 20-0778.

Respectfully submitted,

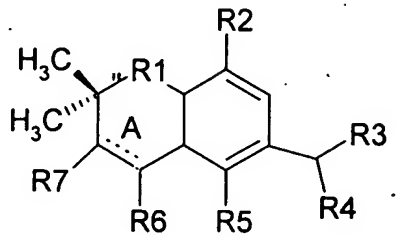


Christopher B. Linder; Reg. No. 47,751
Attorney for Applicant

THOMAS, KAYDEN, HORSTEMEYER & RISLEY, L.L.P.
Suite 1750
100 Galleria Parkway, N.W.
Atlanta, GA 30339-5948
Telephone: (770) 933-9500
Facsimile: (770) 951-0933

We claim:

1. A pharmaceutical composition comprising a compound of formula (I)



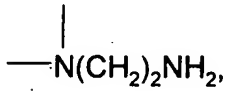
wherein

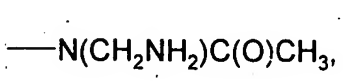
A is a π bond or absent;

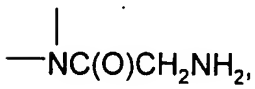
R1 is O, S, or F;

R2 is H, OH, branched or unbranched C_{1-12} alkyl, alkoxy, aryl, heterocycle, imidazole, alkyl substituted aryl, halo substituted aryl, halo, amine, or acyl;

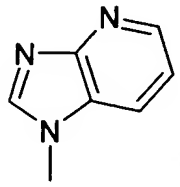
R3 is H, OH, branched or unbranched C_{1-12} alkyl, alkoxy, aryl, heterocycle, imidazole, substituted imidazole, alkyl substituted aryl, halo substituted aryl, halo, amine, acyl , or Z, wherein Z is NH_2,



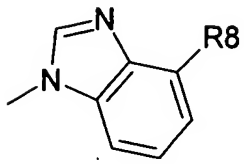




—N(C(O)NH_2)CH_2CH_3,



or



wherein R8 is H,OH, alkyl, alkoxy, or halo;

R4, R6 and R7 are independently H, OH, branched or unbranched C_{1-12} alkyl, alkenyl, alkoxy, aryl, heterocycle, imidazole, substituted imidazole, alkyl substituted aryl, halo substituted aryl, halo, amine, or acyl;

R5 is H, OH, halo, alkyl, or alkoxy; or

a pharmaceutically acceptable salt or prodrug thereof in an amount sufficient to inhibit intracellular HIF-1 activity.

2. A pharmaceutical composition comprising one more compounds selected from the group consisting of

1-[(2,2-dimethyl-2*H*-chromen-6-yl)(phenyl)methyl]-1*H*-imidazole;

1-[(2,2-dimethyl-4a,8a-dihydro-2*H*-chromen-6-yl)(4-methylphenyl)methyl]-1*H*-imidazole;

1-[(2,2-dimethyl-2*H*-chromen-6-yl)(3-methoxyphenyl)methyl]-1*H*-imidazole;

1-[(5-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)(4-methylphenyl)methyl]-1*H*-imidazole;

1-[(2,2-dimethyl-2*H*-chromen-6-yl)(4-fluoro-3-methylphenyl)methyl]-1*H*-imidazole;

1-[(4-chlorophenyl)(2,2-dimethyl-2*H*-chromen-6-yl)methyl]-1*H*-imidazole;

1-[(5-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)(phenyl)methyl]-1*H*-imidazole;

1-[1-(5-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)-3-methylbutyl]-1*H*-imidazole;

1-[(3,3-dimethyl-7,10-dihydro-3*H*-benzo[*f*]chromen-8-yl)(4-fluoro-3-methylphenyl)methyl]-1*H*-imidazole;

1-[(3,3-dimethyl-7,10-dihydro-3*H*-benzo[*f*]chromen-8-yl)(3-methoxyphenyl)methyl]-1*H*-imidazole;

1-[(3,3-dimethyl-7,10-dihydro-3*H*-benzo[*f*]chromen-8-yl)(4-methylphenyl)methyl]-1*H*-imidazole;

1-[(8-methoxy-2,2-dimethyl-2*H*-chromen-7-yl)(phenyl)methyl]-1*H*-imidazo[4,5-*b*]pyridine;

1-[1-(5-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)ethyl]-1*H*-imidazo[4,5-*b*]pyridine;

1-[1-(5-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)-3-methylbutyl]-1*H*-imidazo[4,5-*b*]pyridine;

1-[1-(3,3-dimethyl-7,10-dihydro-3*H*-benzo[*f*]chromen-8-yl)-3-methylbutyl]-1*H*-imidazo[4,5-*b*]pyridine;

4-chloro-1-[cyclohexyl(5-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)methyl]-1*H*-benzimidazole;

1-[cyclohexyl(5-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)methyl]-1*H*-benzimidazole;

1-[1-(2,2-dimethyl-2*H*-chromen-6-yl)prop-2-en-1-yl]-2-methyl-1*H*-benzimidazole;

1-[cyclohexyl(2,2,6-trimethyl-2*H*-chromen-8-yl)methyl]-1*H*-benzimidazole;

(2,2-dimethyl-2*H*-chromen-6-yl)(3-hydroxyphenyl)methyl biphenyl-4-carboxylate;

N-isopropyl-3,4-dimethoxy-*N*-[(8-methoxy-2,2-dimethyl-2*H*-chromen-7-yl)methyl]benzenesulfonamide;

1-[(4-tert-butylphenyl)(2,2-dimethyl-4a,8a-dihydro-2H-chromen-6-yl)methyl]-1H-imidazole;

N-[(2,2-dimethyl-4a,8a-dihydro-2*H*-chromen-6-yl)(phenyl)methyl]-*N*-ethylurea;

N-[(2,2-dimethyl-4a,8a-dihydro-2*H*-chromen-6-yl)(phenyl)methyl]-*N*-methylethane-1,2-diamine;

N-(aminomethyl)-*N*-[(2,2-dimethyl-4a,8a-dihydro-2*H*-chromen-6-yl)(phenyl)methyl]acetamide; and

N^1-[(2,2-dimethyl-4a,8a-dihydro-2*H*-chromen-6-yl)(phenyl)methyl]-N^1-methylglycinamide

in an amount effective to modulate intracellular HIF-1 activity.

3. A pharmaceutical composition comprising a hydrolysis, oxidation, or reduction reaction product of any of the compounds of claims 1 and 2.

4. The pharmaceutical composition of claim 3, wherein the hydrolysis, oxidation, or reduction reaction opens a nitrogen containing ring of any of the compounds of claims 1-2.

5. The pharmaceutical composition of claims 1-4, further comprising a second therapeutic agent.

6. The pharmaceutical composition of claim 5, wherein the second therapeutic agent is an antibiotic, anti-inflammatory, anti-oxidant, analgesic, radioisotope, nascopine, paclitaxel, nocodazole, vinca alkaloids, adriamycin, alkeran, Ara-C, BiCNU, busulfan, CCNU, carboplatinum, cisplatinum, cytoxan, daunorubicin, DTIC, 5-FU, fludarabine, hydrea, idarubicin, ifosfamide, methotrexate, mithramycin, mitomycin, mitoxantrone, nitrogen, mustard, velban, vincristine, VP-16, gemcitabine, herceptin, irinotecan, camptosar, CPT-11, leustatin, navelbine, rituxan, STI-571, taxotere, topotecan, hycamtin, xeloda capecitabine, zevelin, and combinations thereof.

7. A method for the treatment or prevention of a hypoxia-related pathology comprising:

administering to a host in need of such treatment an HIF-1 inhibiting amount of any of the compositions of claims 1-6.

8. A method of modulating HIF-1 activity in a cell comprising: contacting the cell with an HIF-1 inhibiting amount of any of the compositions of claims 1-6.

9. A method of treating or preventing cancer or a tumor in a host comprising administering to the host a HIF-1 inhibiting amount of any of the compositions of claims 1-6.

10. The method of claim 9, wherein the cancer or tumor is selected from the group consisting of bladder cancer, breast cancer, colorectal cancer, endometrial cancer, head & neck cancer, leukemia, lung cancer, lymphoma, melanoma, non-small-cell lung cancer, ovarian cancer, prostate cancer, testicular cancer, uterine cancer, cervical cancer, thyroid cancer, gastric cancer, brain stem glioma, cerebellar astrocytoma, cerebral astrocytoma, ependymoma, Ewing's sarcoma family of tumors,

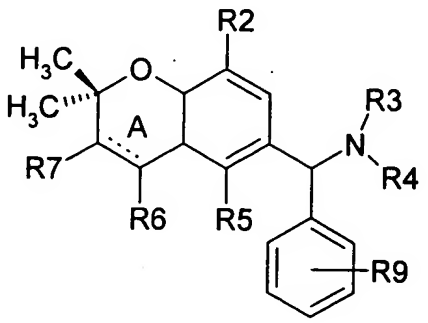
germ cell tumor, extracranial cancer, Hodgkin's disease, leukemia, acute lymphoblastic leukemia, acute myeloid leukemia, liver cancer, medulloblastoma, neuroblastoma, brain tumors generally, non-Hodgkin's lymphoma, osteosarcoma, malignant fibrous histiocytoma of bone, retinoblastoma, rhabdomyosarcoma, soft tissue sarcomas generally, supratentorial primitive neuroectodermal and pineal tumors, visual pathway and hypothalamic glioma, Wilms' tumor, acute lymphocytic leukemia, adult acute myeloid leukemia, adult non-Hodgkin's lymphoma, chronic lymphocytic leukemia, chronic myeloid leukemia, esophageal cancer, hairy cell leukemia, kidney cancer, multiple myeloma, oral cancer, pancreatic cancer, primary central nervous system lymphoma, skin cancer, and small-cell lung cancer.

11. A method of modulating gene transcription in a cell comprising contacting the cell with an HIF-1 inhibiting amount of one or more of the compositions of any of claims 1-6.

12. The method of claim 11, wherein the cell is a cancer cell.

13. The method of claim 11, wherein the gene is VEGF, erythropoietin, glucose transporter-1, glycolytic enzymes, or tyrosine hydroxylase.

14. A pharmaceutical composition comprising a compound of formula (II):

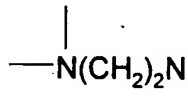


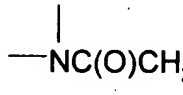
wherein

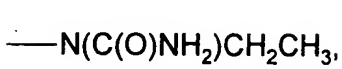
A is a π bond or absent;

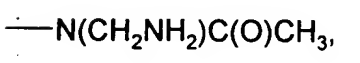
R2 is H, OH, branched or unbranched C_{1-12} alkyl, alkoxy, aryl, heterocycle, imidazole, alkyl substituted aryl, halo substituted aryl, halo, amine, or acyl;

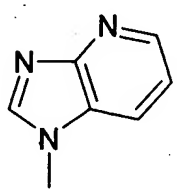
R3 is H, OH, branched or unbranched C_{1-12} alkyl, alkoxy, aryl, heterocycle, imidazole, substituted imidazole, alkyl or alkoxy substituted aryl, halo substituted aryl, halo, amine, acyl , or Z, wherein Z is NH_2,



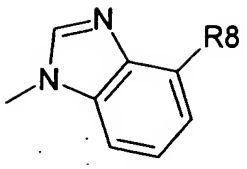








or



wherein R8 is H, OH, alkyl, alkoxy, or halo;

R4, R6, and R7 are independently H, OH, branched or unbranched C_{1-12} alkyl, alkenyl, alkoxy, aryl, heterocycle, imidazole, substituted imidazole, alkyl substituted aryl, halo substituted aryl, halo, amine, acyl;

R5 is H, OH, halo, alkyl, or alkoxy;

R9 is H, OH, halo, alkoxy, alkyl, or aryl; or

a pharmaceutically acceptable salt or prodrug thereof in an amount effective to inhibit HIF-1 intracellular activity.

15. A pharmaceutical composition comprising a hydrolysis, oxidation, or reduction reaction product of the compound of claim 14.

16. The pharmaceutical composition of claim 15, wherein the hydrolysis, oxidation, or reduction reaction opens a nitrogen containing.

17. The pharmaceutical composition of claims 13-16, further comprising a second therapeutic agent.

18. The pharmaceutical composition of claim 17, wherein the second therapeutic agent is an antibiotic, anti-inflammatory, anti-oxidant, analgesic, radioisotope, nascopine, paclitaxel, nocodazole, vinca alkaloids, adriamycin, alkeran, Ara-C, BiCNU, busulfan, CCNU, carboplatinum, cisplatinum, cytoxan,

daunorubicin, DTIC, 5-FU, fludarabine, hydrea, idarubicin, ifosfamide, methotrexate, mithramycin, mitomycin, mitoxantrone, nitrogen, mustard, velban, vincristine, VP-16, gemcitabine, herceptin, irinotecan, camptosar, CPT-11, leustatin, navelbine, rituxan, STI-571, taxotere, topotecan, hycamtin, xeloda capecitabine, zevelin, and combinations thereof.

19. A method for the treatment or prevention of a hypoxia-related pathology comprising:

administering to a host in need of such treatment an HIF-1 inhibiting amount of any of the compositions of claims 14-18.

20. A method of modulating HIF-1 activity in a cell comprising: contacting the cell with an HIF-1 inhibiting amount of any of the compositions of claims 14-18.

21. A method of treating or preventing cancer or a tumor in a host comprising administering to the host a HIF-1 inhibiting amount of any of the compositions of claims 14-18.

22. The method of claim 21, wherein the cancer or tumor is selected from the group consisting of bladder cancer, breast cancer, colorectal cancer, endometrial cancer, head & neck cancer, leukemia, lung cancer, lymphoma, melanoma, non-small-cell lung cancer, ovarian cancer, prostate cancer, testicular cancer, uterine cancer, cervical cancer, thyroid cancer, gastric cancer, brain stem glioma, cerebellar astrocytoma, cerebral astrocytoma, ependymoma, Ewing's sarcoma family of tumors, germ cell tumor, extracranial cancer, Hodgkin's disease, leukemia, acute lymphoblastic leukemia, acute myeloid leukemia, liver cancer, medulloblastoma, neuroblastoma, brain tumors generally, non-Hodgkin's lymphoma, osteosarcoma, malignant fibrous histiocytoma of bone, retinoblastoma, rhabdomyosarcoma, soft tissue sarcomas

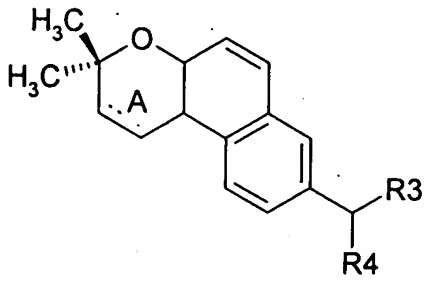
generally, supratentorial primitive neuroectodermal and pineal tumors, visual pathway and hypothalamic glioma, Wilms' tumor, acute lymphocytic leukemia, adult acute myeloid leukemia, adult non-Hodgkin's lymphoma, chronic lymphocytic leukemia, chronic myeloid leukemia, esophageal cancer, hairy cell leukemia, kidney cancer, multiple myeloma, oral cancer, pancreatic cancer, primary central nervous system lymphoma, skin cancer, and small-cell lung cancer.

23. A method of modulating gene transcription in a cell comprising contacting the cell with an HIF-1 inhibiting amount of one or more of the compositions of any of claims 14-18.

24. The method of claim 23, wherein the cell is a cancer cell.

25. The method of claim 23, wherein the gene is VEGF, erythropoietin, glucose transporter-1, glycolytic enzymes, or tyrosine hydroxylase.

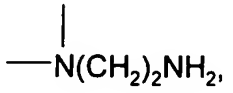
26. A pharmaceutical composition comprising a compound of formula (III):

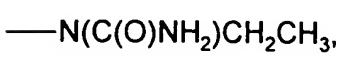


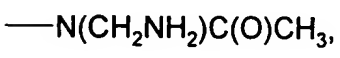
wherein

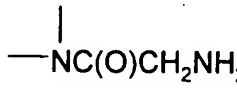
A is a π bond or absent;

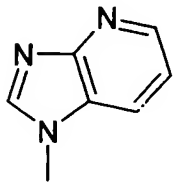
R3 is H, OH, branched or unbranched C_{1-12} alkyl, alkoxy, aryl, heterocycle, imidazole, substituted imidazole, alkyl substituted aryl, halo substituted aryl, halo, amine, acyl , or Z, wherein Z is NH_2,



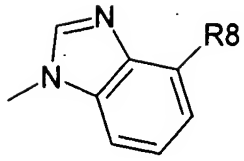








or



68

wherein R8 is H,OH, alkyl, alkoxy, or halo;

R4 is H, OH, branched or unbranched C_{1-12} alkyl, alkenyl, alkoxy, aryl, heterocycle, imidazole, substituted imidazole, alkyl substituted aryl, halo substituted aryl, halo, amine, acyl; or

a pharmaceutically acceptable salt or prodrug thereof, in an amount effective to inhibit intracellular HIF-1 activity.

27. A pharmaceutical composition comprising a hydrolysis, oxidation, or reduction reaction product of the compound of claim 26.

28. The pharmaceutical composition of claim 27, wherein the hydrolysis, oxidation, or reduction reaction opens a nitrogen containing.

29. The pharmaceutical composition of claims 26-28, further comprising a second therapeutic agent.

30. The pharmaceutical composition of claim 29, wherein the second therapeutic agent is an antibiotic, anti-inflammatory, anti-oxidant, analgesic, radioisotope, nascopine, paclitaxel, nocodazole, vinca alkaloids, adriamycin, alkeran, Ara-C, BiCNU, busulfan, CCNU, carboplatinum, cisplatinum, cytoxan, daunorubicin, DTIC, 5-FU, fludarabine, hydrea, idarubicin, ifosfamide, methotrexate, mithramycin, mitomycin, mitoxantrone, nitrogen, mustard, velban, vincristine, VP-16, gemcitabine, herceptin, irinotecan, camptosar, CPT-11, leustatin, navelbine, rituxan, STI-571, taxotere, topotecan, hycamtin, xeloda capecitabine, zevelin, and combinations thereof.

31. A method for the treatment or prevention of a hypoxia-related pathology comprising:

administering to a host in need of such treatment an HIF-1 inhibiting amount of any of the compositions of claims 26-30.

32. A method of modulating HIF-1 activity in a cell comprising: contacting the cell with an HIF-1 inhibiting amount of any of the compositions of claims 26-30.

33. A method of treating or preventing cancer or a tumor in a host comprising administering to the host a HIF-1 inhibiting amount of any of the compositions of claims 26-30.

34. The method of claim 33, wherein the cancer or tumor is selected from the group consisting of bladder cancer, breast cancer, colorectal cancer, endometrial cancer, head & neck cancer, leukemia, lung cancer, lymphoma, melanoma, non-small-cell lung cancer, ovarian cancer, prostate cancer, testicular cancer, uterine cancer, cervical cancer, thyroid cancer, gastric cancer, brain stem glioma, cerebellar astrocytoma, cerebral astrocytoma, ependymoma, Ewing's sarcoma family of tumors, germ cell tumor, extracranial cancer, Hodgkin's disease, leukemia, acute lymphoblastic leukemia, acute myeloid leukemia, liver cancer, medulloblastoma, neuroblastoma, brain tumors generally, non-Hodgkin's lymphoma, osteosarcoma, malignant fibrous histiocytoma of bone, retinoblastoma, rhabdomyosarcoma, soft tissue sarcomas generally, supratentorial primitive neuroectodermal and pineal tumors, visual pathway and hypothalamic glioma, Wilms' tumor, acute lymphocytic leukemia, adult acute myeloid leukemia, adult non-Hodgkin's lymphoma, chronic lymphocytic leukemia, chronic myeloid leukemia, esophageal cancer, hairy cell leukemia, kidney cancer,

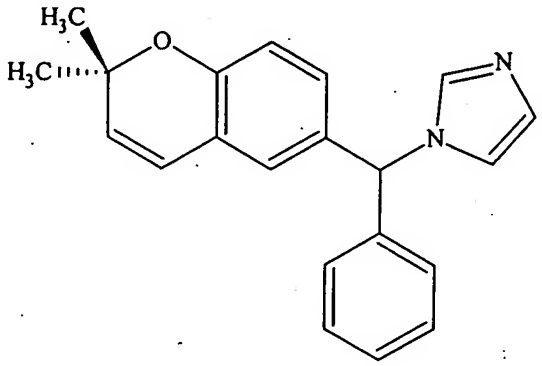
multiple myeloma, oral cancer, pancreatic cancer, primary central nervous system lymphoma, skin cancer, and small-cell lung cancer.

35. A method of modulating gene transcription in a cell comprising contacting the cell with an HIF-1 inhibiting amount of one or more of the compositions of any of claims 26-30.

36. The method of claim 35, wherein the cell is a cancer cell.

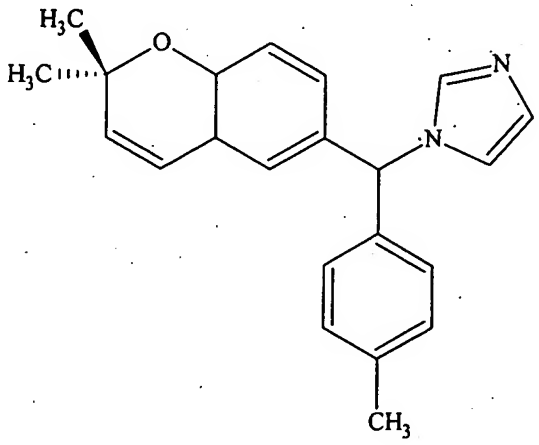
37. The method of claim 35, wherein the gene is VEGF, erythropoietin, glucose transporter-1, glycolytic enzymes, or tyrosine hydroxylase.

38. A compound of the formula:



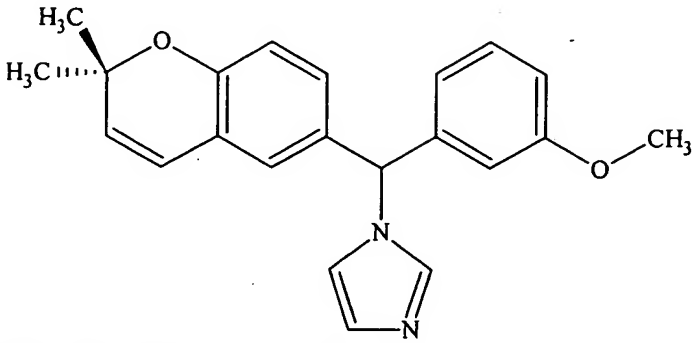
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

39. A compound of the formula:



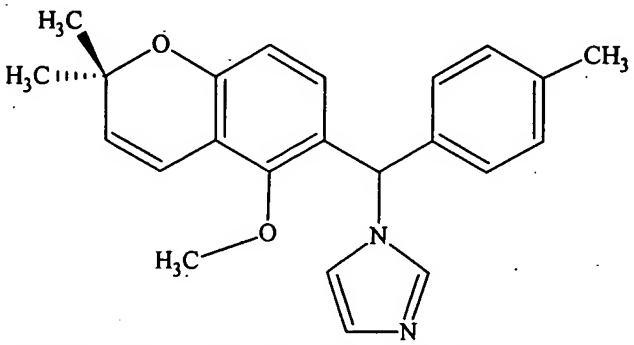
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

40. A compound of the formula:



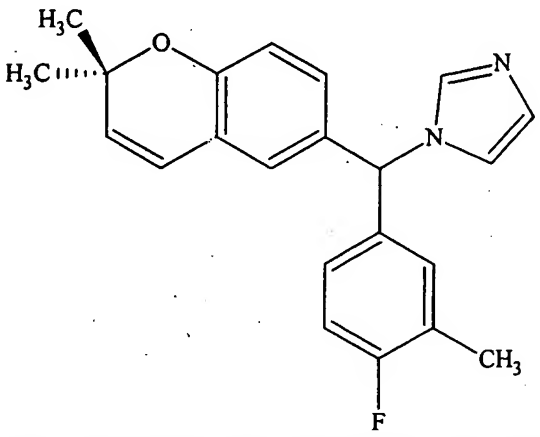
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

41. A compound of the formula:



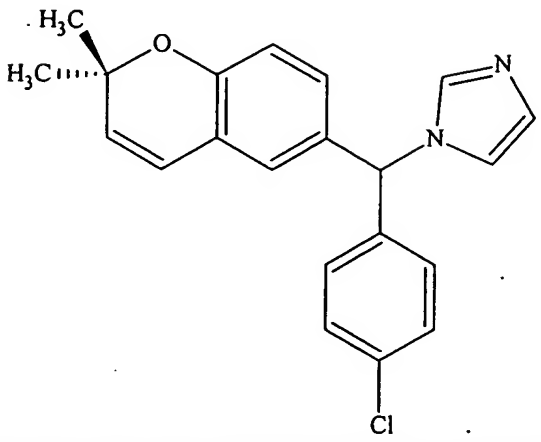
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

42. A compound of the formula:



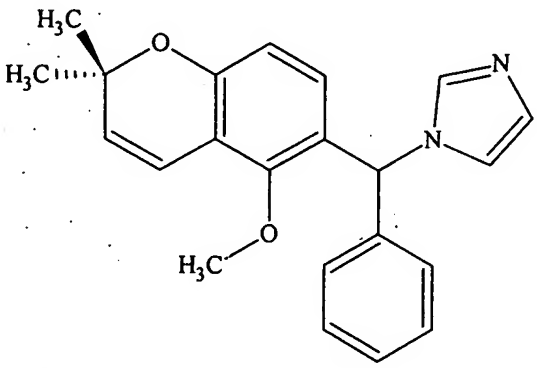
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

43. A compound of the formula:



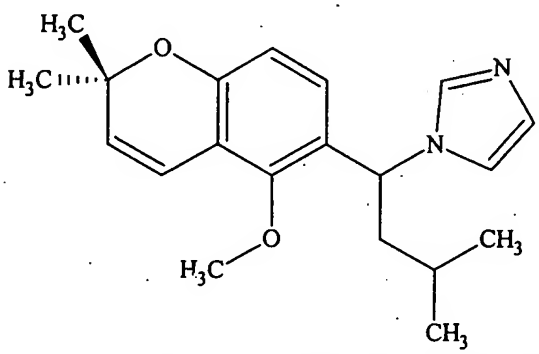
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

44. A compound of formula:



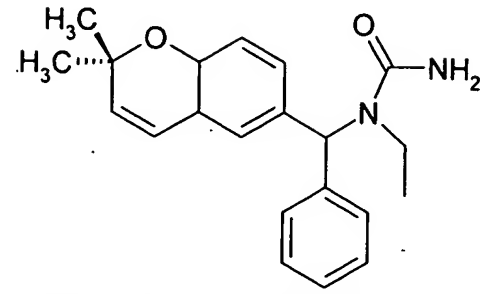
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

45. A compound of the formula:



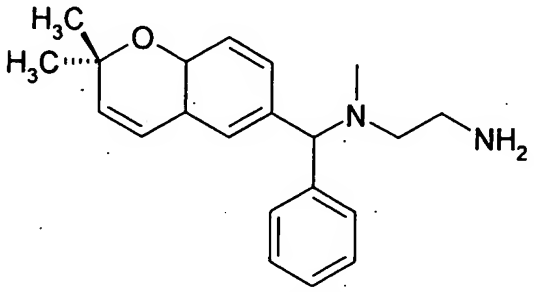
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

46. A compound of the formula:



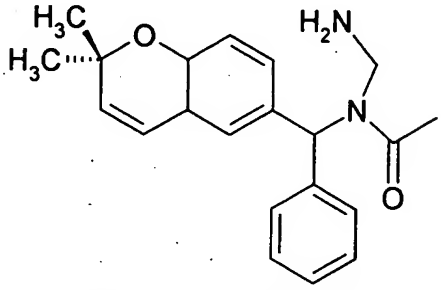
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

47. A compound of the formula:



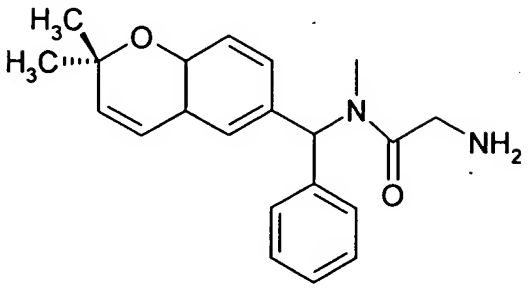
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

48. A compound of the formula:



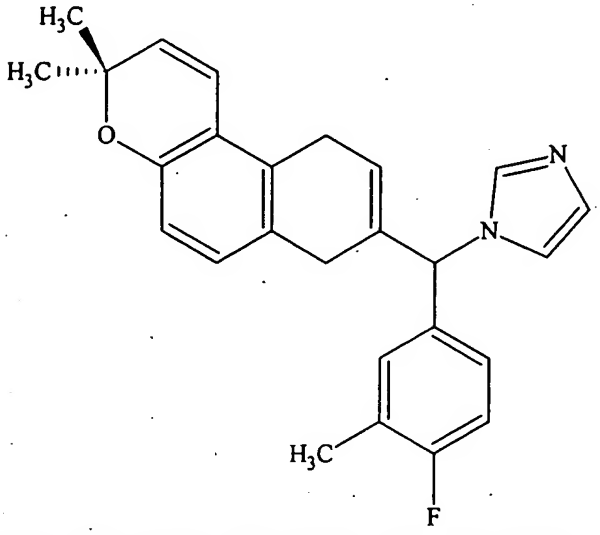
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

49. A compound of the formula:



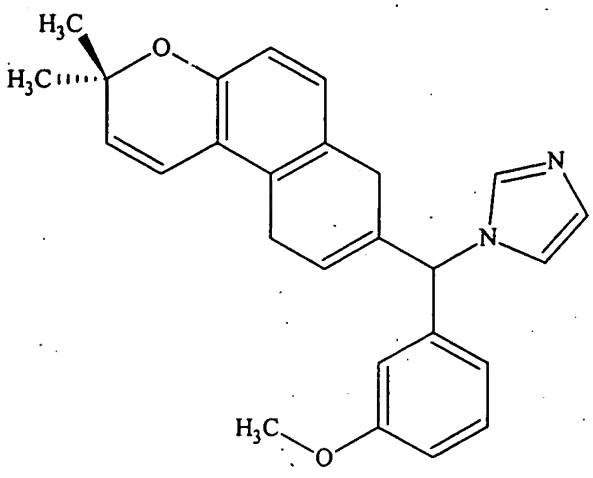
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

50. A compound of the formula:



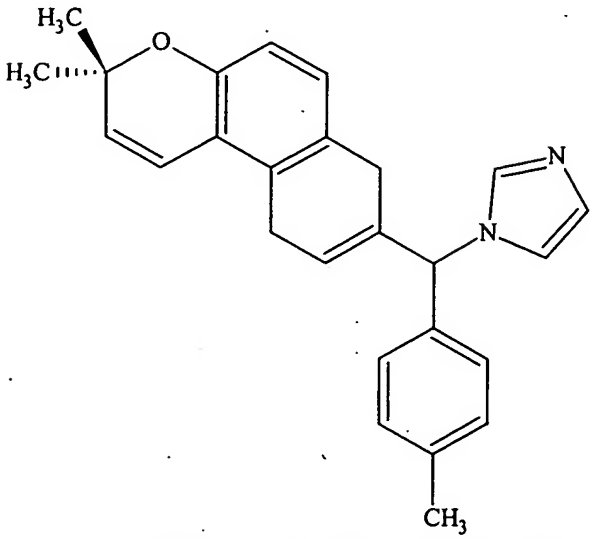
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

51. A compound of the formula:



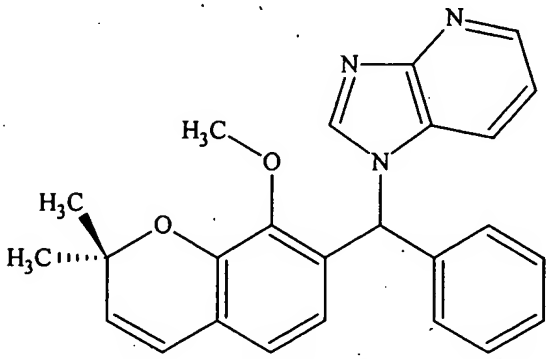
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

52. A compound of the formula:



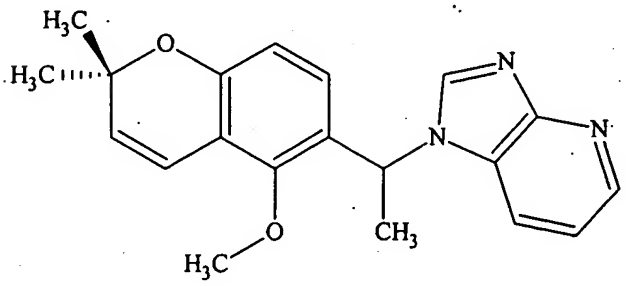
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

53. A compound of the formula:



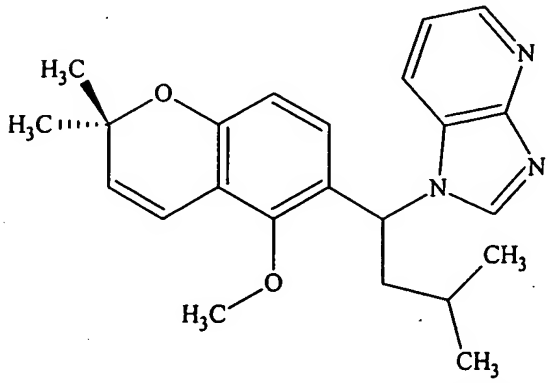
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

54. A compound of the formula:



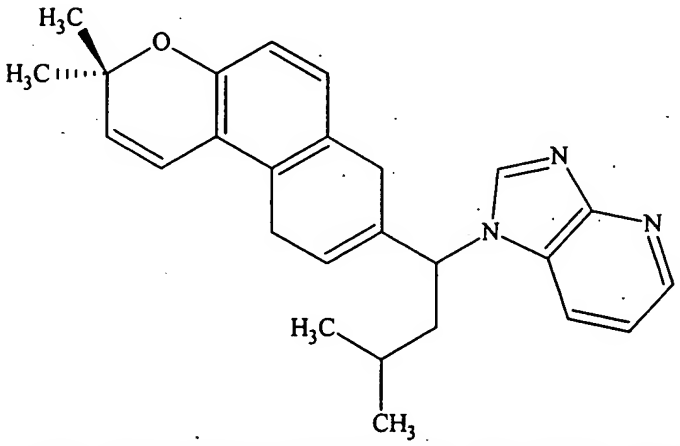
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

55. A compound of the formula:



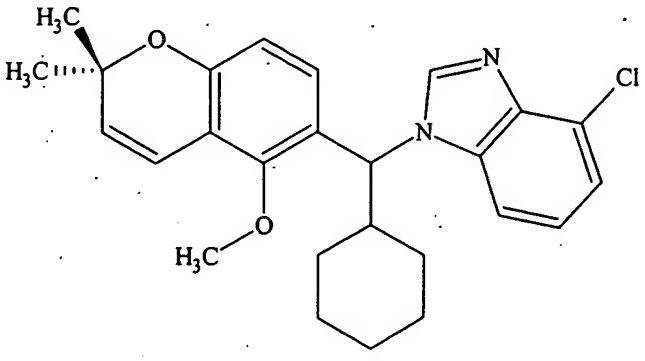
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

56. A compound of the formula:



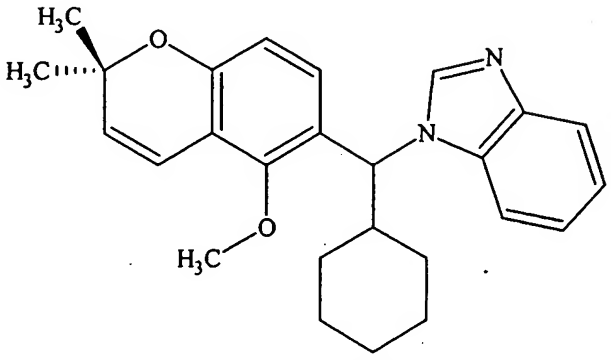
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

57. A compound of the formula:



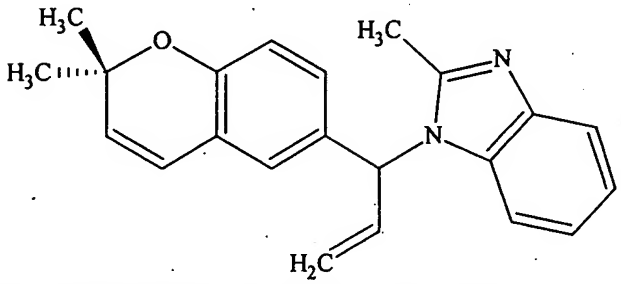
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

58. A compound of the formula:



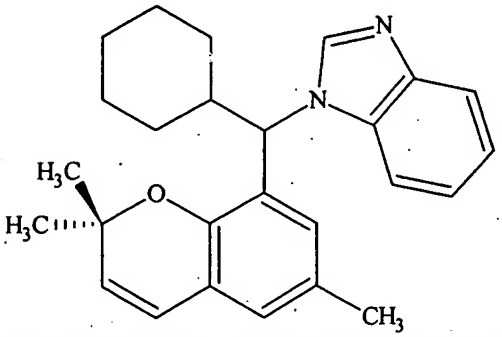
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

59. A compound of the formula:



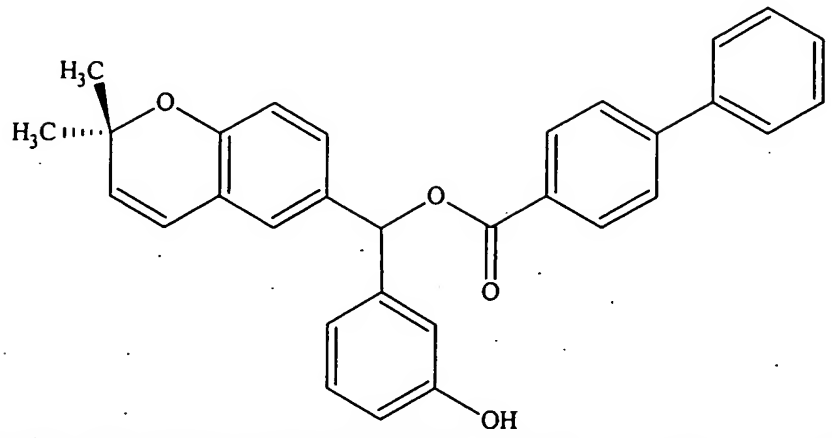
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

60. A compound of the formula:



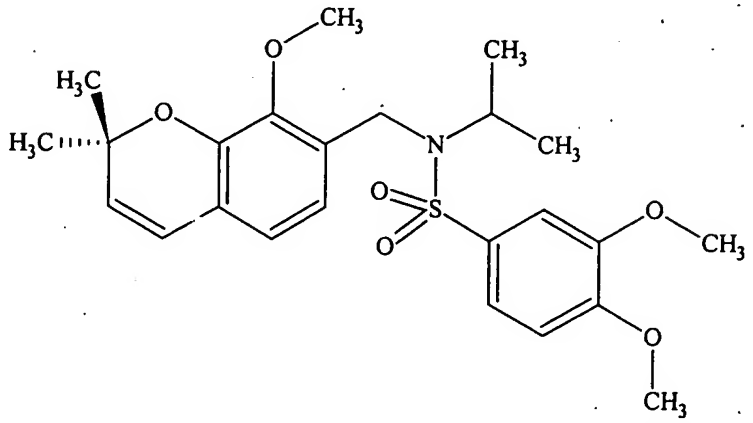
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

61. A compound of the formula:



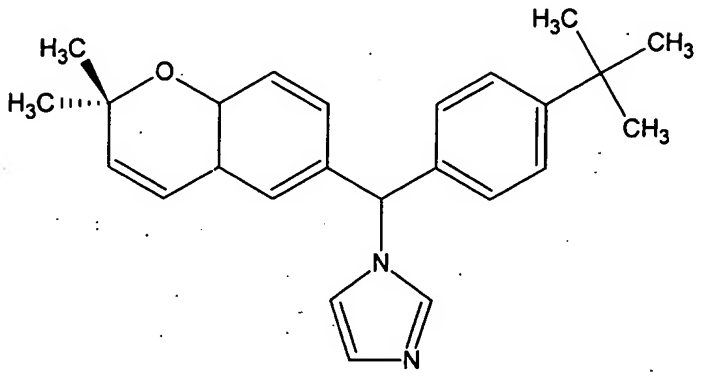
or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

62. A compound of the formula:



or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

63. A compound of the formula:



or a pharmaceutically acceptable salt, derivative, or prodrug thereof.

64. A pharmaceutical composition comprising a compound of any of claims 38-63 or a combination thereof.

65. A pharmaceutical composition comprising a hydrolysis, oxidation, or reduction reaction product of the compound of claims 38-63.

66. The pharmaceutical composition of claim 65, wherein the hydrolysis, oxidation, or reduction reaction opens a nitrogen containing.

67. The pharmaceutical composition of claim 64, further comprising a second therapeutic agent.

68. The pharmaceutical composition of claim 67, wherein the second therapeutic agent is an antibiotic, anti-inflammatory, anti-oxidant, analgesic, radioisotope, nascopine, paclitaxel, nocodazole, vinca alkaloids, adriamycin, alkeran, Ara-C, BiCNU, busulfan, CCNU, carboplatinum, cisplatinum, cytoxan, daunorubicin, DTIC, 5-FU, fludarabine, hydrea, idarubicin, ifosfamide, methotrexate, mithramycin, mitomycin, mitoxantrone, nitrogen, mustard, velban, vincristine, VP-16, gemcitabine, herceptin, irinotecan, camptosar, CPT-11, leustatin, navelbine, rituxan, STI-571, taxotere, topotecan, hycamtin, xeloda capecitabine, zevelin, and combinations thereof.

69. A method for the treatment or prevention of a hypoxia-related pathology comprising:

administering to a host in need of such treatment an HIF-1 inhibiting amount of any of the compositions of claims 38-67.

70. A method of modulating HIF-1 activity in a cell comprising: contacting the cell with an HIF-1 inhibiting amount of any of the compositions of claims 38-67.

71. A method of treating or preventing cancer or a tumor in a host comprising administering to the host a HIF-1 inhibiting amount of any of the compositions of claims 38-67.

72. The method of claim 71, wherein the cancer or tumor is selected from the group consisting of bladder cancer, breast cancer, colorectal cancer, endometrial cancer, head & neck cancer, leukemia, lung cancer, lymphoma, melanoma, non-small-cell lung cancer, ovarian cancer, prostate cancer, testicular cancer, uterine cancer, cervical cancer, thyroid cancer, gastric cancer, brain stem glioma, cerebellar astrocytoma, cerebral astrocytoma, ependymoma, Ewing's sarcoma family of tumors, germ cell tumor, extracranial cancer, Hodgkin's disease, leukemia, acute lymphoblastic leukemia, acute myeloid leukemia, liver cancer, medulloblastoma, neuroblastoma, brain tumors generally, non-Hodgkin's lymphoma, osteosarcoma, malignant fibrous histiocytoma of bone, retinoblastoma, rhabdomyosarcoma, soft tissue sarcomas generally, supratentorial primitive neuroectodermal and pineal tumors, visual pathway and hypothalamic glioma, Wilms' tumor, acute lymphocytic leukemia, adult acute myeloid leukemia, adult non-Hodgkin's lymphoma, chronic lymphocytic leukemia, chronic myeloid leukemia, esophageal cancer, hairy cell leukemia, kidney cancer, multiple myeloma, oral cancer, pancreatic cancer, primary central nervous system lymphoma, skin cancer, and small-cell lung cancer.

73. A method of modulating gene transcription in a cell comprising contacting the cell with an HIF-1 inhibiting amount of one or more of the compositions of any of claims 38-67.

74. The method of claim 73, wherein the cell is a cancer cell.

75. The method of claim 73, wherein the gene is VEGF, erythropoietin, glucose transporter-1, glycolytic enzymes, or tyrosine hydroxylase.